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THIP treatment of Huntington's disease

Article abstract—We evaluated the therapeutic efficacy of gamma aminobutyric acid (GABA) system stimulation in four patients with classical Huntington's disease and one with the hypokinetic-rigid form. Orally administered THIP (4,5,6,7-tetrahydroisoxazolo-[5,4,-c] pyridin-3-ol), a novel GABA receptor agonist, failed to improve motor or cognitive function during a 2-week trial. At maximum levels, THIP mimicked another putative GABA agonist, muscimol, in causing unsteadiness of gait, diminished attention to sensory stimuli, and somnolence. These effects suggest that central GABA systems participate in the regulation of some human and behavioral functions. CSF content of homovanillic acid, a major metabolite of dopamine, increased during high-dose THIP therapy, suggesting that augmentation of dopaminergic function may have contributed to the drug's lack of efficacy.

NEUROLOGY (Cleveland) 1983;33:637-9

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The basal ganglia content of gamma aminobutyric acid (GABA) is reduced in patients with Huntington's disease.[1] Striatal application of drugs that antagonize GABA can induce involuntary movements,[2] and pharmacologic agents that stimulate GABA-mediated synaptic function tend to suppress naturally occurring or drug-induced hyperkinetic disorders.[3,4] Although previous attempts to treat Huntington's disease with drugs that enhance central GABA activity have been unsuccessful, the recent development of THIP (4,5,6,7-tetrahydroisoxazolo-[5,4,-c]pyridin-3-ol) provided an opportunity to test the therapeutic efficacy of a relatively more specific and presumably less toxic GABA analog.

Patients and methods. Five patients (two men and three women aged 25 to 59 years) with Huntington's disease gave informed consent. Four had the classical form with chorea and dementia (one mild, one moderate, and two severe); the fifth had dementia with mild rigidity and tremor (hypokinetic-rigid form). All had a family history of Huntington's disease and CT evidence of caudate atrophy. There was no evidence of other significant illness, and none of the subjects received other medications during this clinical trial. Two patients who had been taking phenothiazines were drug-free for 2 weeks before entering the study.

A double-blind crossover design was used with initial and terminal placebo phases of random length. Each patient received four identical capsules containing either THIP or an inert placebo (supplied by H. Lundbeck and Co., Copenhagen, Denmark) four times daily for 30 days. THIP was begun at a daily dose of 15 mg, and was gradually increased to a maximum of 60 to 120 mg. The duration of placebo averaged 10 days, and that of active drug therapy 14 days.

Motor and behavioral function was assessed periodically at the bedside by one or more blinded observers. One hour after the first morning THIP dose, extrapyramidal function was evaluated, using the Abnormal Involuntary Movement Scale (AIMS) and the modified Columbia rating scale.[5,6] Videotaped records provided a subsequent opportunity to validate these ratings. Memory was evaluated by a word-learning test consisting of an eight-noun list recited in five trials; a different set of words was given in each assessment. Reaction time was measured by the time necessary to depress a telegraph key after an auditory cue. The Brief Psychiatric Rating Scale (BPRS)[7] was used to evaluate behavioral changes.

CSF was obtained by lumbar puncture before treatment was initiated and again at the highest tolerated dose of THIP. The timing of the CSF examination was unknown to the blinded observers. Fluid was collected on ice; 1-ml aliquots of the first 13 ml were frozen at 70 °F within 1 hour for later analysis. GABA was assayed, using an ion-exchange fluorometric technique, after being deproteinized by adding 1/3 volume of 20% aqueous sulfosalicylic acid.[8] Homovanillic acid (HVA), a metabolite of dopamine, was determined by high-performance liquid chromatography with an electrochemical detector.[9]

Results. There was no clinically significant improvement in abnormal involuntary movements during THIP treatment. Although AIMS scores indicated that chorea was somewhat reduced in several patients at moderate THIP dose levels, for the group as a whole this change failed to reach statistical significance (table 1). Parkinsonian signs remained unchanged by the Columbia rating scale in the rigid patient. Behavioral testing revealed no consistent alteration at less than maximal doses in word learning (5.2 ± 0.5 words recalled on placebo and 5.2 ± 0.4 during treatment), reaction time (0.416 ± 0.09 msec versus 0.401 ± 0.04), or BPRS scores (25 ± 1.7 versus 24 ± 0.6).

Table 1. Effect of THIP on AIMS* score

Pt no.	Placebo	60 mg per day	% improvement
1	10	8	20
2	33	32	3
3	34	30	12
4	21	21	0
5	6	5	17
Mean ± SEM	21 ± 5.7	19 ± 5.5	10 ± 3.9

* The Abnormal Involuntary Movement Scale (AIMS) was used to assess motor function.

The GABA content of plasma (231 ± 3 pmol per milliliter before and 224 ± 21 during treatment) or CSF (table 2) showed no significant change, but CSF HVA increased by an average of 25% ($p < 0.05$).

At maximum THIP doses (60 to 120 mg per day), all patients evidenced temporary unsteadiness of gait, and four of five had some worsening of involuntary movements. In addition, there was a transitory alteration in consciousness in every patient. All manifested periods of mild somnolence, and during alert periods all developed a dissociative state with slow responses to external stimuli. Amnesia for events during the dissociative state was common. One individual also reported hypnogogic hallucinations. Vital signs and routine tests of renal, hepatic, and hematologic function remained within normal limits.

Discussion. Attempts to provide symptomatic relief to patients with Huntington's disease through pharmacologic stimulation of the GABA system have proved disappointing. An initial report of a response to isoniazid, which inhibits GABA degradation by GABA transaminase (GABA-T), was not confirmed by controlled investigations.[10-12] Other inhibitors of GABA-T, including gamma-vinyl GABA[13] and amino-oxyacetic acid,[14] have also been ineffective. Similarly, GABA agonists such as imidazole-4-acetic acid[15] and muscimol[16] have lacked therapeutic activity or induced significant toxicity. Finally, THIP also failed to provide clinical improvement during our brief study, although effects of long-term treatment must await other trials.

THIP was selected because of several potentially favorable pharmacokinetic and pharmacologic properties. THIP is completely absorbed when given orally, crosses the blood-brain barrier more completely than muscimol, and is primarily excreted unchanged.[17,18] Moreover, the binding character-

Table 2. Effect of THIP on CSF GABA and HVA

	GABA			HVA		
Pt no.	Baseline (pmol/ml)	Treatment (pmol/ml)	% increase	Baseline (ng/ml)	Treatment (ng/ml)	% increase
2	103	133	29	18	21	17
3	160	193	21	12	18	50
4	111	135	22	18	21	17
5	113	100	−11	31	36	16
Mean ± SEM	122 ± 13	140 ± 19	15 ± 8.9	20 ± 4.0	24 ± 4.1	25 ± 8*

Treatment values obtained at an average daily THIP dose of 100 mg.
* $p < 0.05$ t-test for paired data.

istics of THIP differ from those of muscimol or other GABA agonists currently available for study.[19,20]

The motor and behavioral changes during THIP therapy suggest that the drug is capable of penetrating the human brain. Moreover, some of the transient effects induced by high doses of THIP resembled those observed with another potent GABA agonist, muscimol.[16,21,22] These effects included unsteadiness and an altered state of consciousness characterized by a peculiar inattentiveness to external stimuli or by somnolence, suggesting that GABA-containing neuronal systems may contribute to the regulation of some human psychomotor functions.

It is notable that the highest values of HVA seen among our patients were found in the person with hypokinetic-rigid features. So far, no consistent difference in HVA concentration has been documented in this as compared with the more typical form of Huntington's disease.

Although examined only in four patients, the finding of increased CSF HVA levels may indicate that THIP augments central dopaminergic function. In rats, THIP elevated striatal and limbic HVA concentrations and nigral and ventral tegmental dopamine neuron firing rates.[23,24] Since drugs that potentiate dopamine-mediated synaptic transmission characteristically aggravate chorea, the lack of effectiveness of THIP in Huntington's disease may be attributed to direct or indirect actions on the dopamine system. Whether this or some other possibility, such as a loss of GABA receptors or the multiplicity of transmitter systems that degenerate, accounts for the inability of THIP to ameliorate symptoms of Huntington's disease remains to be determined.

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Accepted for publication August 17, 1982.

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